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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/147,346	03/01/1999	SHAI YARKONI	1268-073	1591

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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/147,346	YARKONI ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE f this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,10 and 21-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10 and 21-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1, 29, have been amended.

Claims 30-35 have been added.

Claims 1-7, 9-10, 21-35 are pending and under examination.

2. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

3. The following Office Action contains NEW GROUNDS of rejection.

Rejections Withdrawn

4. The rejection of claims 9-10, 22 under 35 U.S.C. 103(a) as being unpatentable over Nett et al (U.S. Patent 5,378,688, issued 1/95), and further in view of Chaudhary et al {a} (Nature 339:394-397, 1989, PTO-892 paper #11) and Chaudhary et al {b} (Proc. Natl. Acad. Sci. USA 84:4538-4542, 1987, PTO-892, paper #11) and as evidenced by the specification is withdrawn in view of the declaration of Haya Lorberboum-Galski demonstrating that the GnRH-PE can be used to target and treat adnocarcinomas.

5. The rejection of claims 1-7, 9-10, 21-29 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims and arguments.

Response to Arguments

6. The rejection of claims 1-7, 21, 23-29 and newly added claims 30-35 under 35 U.S.C. 103(a) as being unpatentable over Nett et al (U.S. Patent 5,378,688, issued 1/95), and further in view of Chaudhary et al {a} (Nature 339:394-397, 1989, PTO-892 paper #11) and Chaudhary et al {b} (Proc. Natl. Acad. Sci. USA 84:4538-4542, 1987, PTO-892, paper #11) and as evidenced by the specification is maintained.

The response filed 8/4/03 and 6/16/03 have been carefully considured but are deemed not to be persuasive. The response states that the prior art proteins and the claimed proteins are different biological molecules and are not obvious from one another and each GnRH-PE claimed is a single molecule and using conventional chemistry the molecules of Nett et al would have multiple ligand attachment sites and have a mixture of products and using only 10 amino acids such as GnRH in the chimeric protein claimed is not obvious and to the best of applicants knowledge a peptide of ten amino acids has never before been proposed or used in construction of a chimeric protein (see page 8 -10 of response of 6/16/03). In response to this argument, when combining the prior art one would obviously obtain a molecule that is a chimeric comprising the 10 amino acids of GnRH fused to PE and this molecule would be identical to the claimed molecules. It would not be constructed chemically or synthetically. The rejection uses Nett et al GnRH and prepares the conjugate according to Chaudhary et al which would result in the claimed molecule and have all the properties recited such as recognizing cells bearing the binding sites. In addition, Nett et al clearly teaches a 10 amino acid peptide in construction of a chimeric protein and as such it is unclear how applicants have no knowledge of this construction and is not

innovative because the prior art teaches such a construct. The response further states that the conjugates recognize and target different receptors and the GnRH-based chimeric protein target and kill adenocarcinoma cells and this is demonstrated in the declaration of Haya Lorberboum-Galski (see page 10-13 of response). In response to this argument, the declaration has been carefully considured but is deemed not to be persuasive because the molecules that would result from the combination of Nett et al and Chaudary et al would be the same as those claimed and as such would obviously target the adenocarcinoma cells binding sites. The product claimed and the products produced by the combination of the prior art would result in targeting the binding sites on adenocarcinoma cells because the products are the same, GnRH-PE conjugates.

The following are NEW GROUNDS of rejection

Claim Rejections - 35 USC § 112

7. Claims 30-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 3034 are indefinite for reciting "starting with Meth and having a glycine as the sixth amino acid" because it is unclear how the protein can start with Meth at position one and have a glycine at the sixth position. As evidenced from Nett et al US patent 5,378,688 column 8, GnRh is a decapeptide with glycine at the sixth position.

The GnRH does not have a Meth and as such adding the Meth results in the glycine at position 7 not 6. Therefore it is not clear what position the glycine should be.

Claim Rejections - 35 USC § 103

8. Claims 1-7, 9-10, 21-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nett et al (U.S. Patent 5,378,688, issued 1/95), and further in view of Chaudhary et al {a} (Nature 339:394-397, 1989, PTO-892 paper #11) and Chaudhary et al {b} (Proc. Natl. Acad. Sci. USA 84:4538-4542, 1987, PTO-892, paper #11) and Imai et al (Cancer 74:2555-61, 1994) and as evidenced by the specification.

The claims are summarized as a targeted fused chimeric toxin comprising a genetically engineered molecule fused at the cDNA level of an moiety encoding 10 amino acids of GnRH and PE wherein the PE is PE66 or PE40 and starting with Meth wherein the toxin binds to GnRH on adenocarcinoma cells and a method of producing such and a method comprising administering the chimeric toxin to adenocacinoma cells and a method of treating endometriosis, uterine myoma, pituitary adenoma, BPH, and polycystic breast disease with administration of the chimeric toxin.

Nett et al teach conjugation of gonadotropin releasing hormone (GnRH) to toxins and the GnRH is used to target cells bearing GnRH binding sites and the toxin is employed to permanently destroy cells. Nett et al also teach compositions comprising such proteins. Nett et al also teach the ten amino acids of GnRH targeted protein (see column 8 where Z can be Gly-NH2). Nett et al also teach modifications to the sequence

of GnRH at positions 6 and 10 which result in higher affinity for the GnRH receptor that are 100 times more potent than the parent compound (see column 5 and 8) as well as chemically altering the GnRH molecule. Nett et al also teach production of the toxins by recombinant DNA technology and the toxin can be PE (see column 14) and administering the conjugated toxins to animals intravenously (see column 13). Nett et al also teach the GnRH/toxin conjugates can be used for treating cancer of the prostate and breast and endometriosis (see column 12, lines 58-65 and column 13, lines 20-29). Nett et al does not teach (1) a plasmid or (2) methods for ligating the oligonucleotide encoding GnRH or a toxin to produce a chimeric toxin molecule or a mutated form of PE or PE encoding for domains I and II or methods using a recombinant chimeric toxin or (3) GnRH receptor on adenocarcinoma cells. These deficiencies are made up in the teachings of Chaudhary et al {a} and {b} and Imai et al.

Chaudhary et al {a} teach a chimeric toxin comprising an immunoglobulin and a mutated form of PE consisting of domains I and II of PE in which PE is the toxic moiety (designated PE-40) and a plasmid which comprises ligating the DNA encoding for the immunoglobulin single chain upstream of the PE wherein said plasmid contains a promoter operably linked to the molecule encoding for such chimeric toxin (see Figure 1 and page 395). Chaudhary et al {a} also teach a method of producing a fusion protein toxin and methods of treating cancer.

Chaudhary et al {b} teach a recombinant fusion protein comprising transforming growth factor type alpha and PE 40 wherein PE 40 consists of domains II and III (see Figure 1 and Figure 2). Chaudhary et al {b} also teach a method of producing said

fusion protein with recombinant methods and a plasmid comprising a promoter and an in vitro method of treating cancer cells (see page 4539, Assay of the Biological activity).

Imai et al teach the GnRH receptor on adenocarcinoma cells, endometrial carcinomas and other cancers and using GnRH analogs for therapy for malignancies.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a fusion protein comprising the ten amino acids of GnRH, wherein residue(s) have been substituted in GnRH, wherein the oligonucleotide encoding for GnRH is ligated upstream to DNA encoding a mutated form of PE, wherein the fusion protein is produced by recombinant methods, wherein the plasmid encoding for such comprises a promoter, a method for producing such, compositions comprising such, and a method for administering said compositions to a patient for treatment of cancer.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produce the claimed invention because Nett et al teach the amino acid sequence of the GnRH (see column 5 and 8). Nett et al also teach a reason to mutate the GnRH at positions 6 and 10 to produce compounds that have higher affinity for the GnRH receptor. In addition, Nett et al teach the use of fusion protein toxins has utility in human medicine for treatment of cancer. One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produce the claimed invention because Chaudhary et al {a} teach recombinant DNA techniques have been used to produce chimeric toxin fusion proteins in E. coli. and Chaudhary et al fused the "targeting moiety" upstream of the PE toxin

(See page 395 and Figure 1). One of ordinary skill in the art would also have been motivated to and had a reasonable expectation of success to have produce the claimed invention because Chaudhary et al {b} teach "A PE molecule which domain I has been deleted (PE40) has full ADP-ribosylation activity but has extremely low cell-killing activity because of loss of the cell-recognition domain" (see page 4538) and "We have now began to use PE40 to construct chimeric proteins in which growth factor genes or other genes have been replaced domain I to impart new and specific cell recognition properties" (see page 4538). In addition, One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produce the claimed invention by recombinant DNA techniques because Chaudhary et al {b} teach chemical conjugation of proteins to toxins result in nonspecific toxicity due to incomplete inactivation of domain I and this nonspecific toxicity is much diminished in genetically engineered chimeric PE40 toxin fusion proteins. (See page 4542). Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produce the claimed invention because Chaudhary et al {b} teach the fusion toxin protein targeted cancer cells and resulted in cell killing activity. Also one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produce the claimed invention because Imai et al teach the GnRH receptor on adenocarcinoma cells and endometrial and myomas and other carcinomas and the GnRH can be used as therapy as well as analogs can be used in combinational therapy (see abstract and page 2560). Finally, one of ordinary skill in the art would also have been motivated and had a reasonable expectation of success to

use the chimeric toxins in method to target adenocarcinoma cells because as evidenced by the specification it was known in the art that GnRH analogs have been demonstrated to be effective in several carcinomas of the breast, prostate, pancreas, endometrial, and ovarian (see page 2 of the specification). Finally, it is well known in the art that ATG (which codes for Meth) would be needed as the initiation codon for the protein to be produced and it would have been obvious to add a Meth on the N-terminus for expression of the protein.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 6/16/03 has been carefully considured but is deemed no to be persuasive. The response states that the declaration submits evidence that support the difference between the protein claimed and the molecules of the references and the receptors are different on the adenocarcinoma cells and the mechanism of action is different for the molecules of the invention and the GnRH chimeric proteins specifically target and kill only adenocarcinoma cells (see pages 10-13). In response to these arguments, Imai et al specifically teach the GnRH binding sites on adenocarcinoma cells and the GnRH targets the cells and conventional therapy can be used to treat cancer which in view of Chaudhary et al who teaches PE toxins for targeting cancer, it would have been obvious to target adenocarcinoma cells with the conjugate. In addition, the adenocarcinoma cells would be targeted and killed because the cells express the binding site as well as other cells as taught be Imai et al.

9. Claims 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 33 and 34 have been amended to recite "that has no linking moiety between said killing moiety and said cell killing moiety" in claim 33 and "wherein said linking moiety is a linear protein" in claim 34. The response filed 6/16/03 and 8/4/03 did not state where support can be found for the claims or claimed limitations. While the specification discloses a direct conjugate (with no linker of a chemical or a protein) of GnRH and PE (see figure 1), there appears no support for a linking moiety being a linear protein or support to exclude all linking moieties. Applicant is required to provide specific support for the claimed limitations in the specification as originally filed or remove them from the claims.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00

am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, PH.D
PRIMARY EXAMINER